

Targeted Photoimmunotherapy Approach for Cancer Moves Forward

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Two new studies from NCI researchers add to growing evidence of the promise of a novel type of cancer immunotherapy that uses infrared light to activate rapid and selective killing of cancer cells.

One of the studies, [presented](#) last week at the American Association for Cancer Research (AACR) annual meeting in New Orleans, showed that this approach, called near-infrared photoimmunotherapy (NIR-PIT), could unleash immune activity against tumors in mice by depleting the tumor microenvironment of certain immune cells that act to restrain the immune response against tumors.

The other [study](#), published March 10 in *Oncotarget*, showed that, in both cells in culture and mice, NIR-PIT specifically targets cancer cells or tumors that express mesothelin, a cell-surface protein that is present at high levels in several aggressive human cancers, including mesothelioma, pancreatic cancer, and ovarian cancer.

An early-phase clinical trial of NIR-PIT is already underway in people with recurrent head and neck cancers, which overexpress the epidermal growth factor receptor EGFR1.

Killing Cancer Cells with the Help of Infrared Light – Photoimmunotherapy



Near-infrared photoimmunotherapy uses an antibody-photoabsorber conjugate that binds to cancer cells. When near-

infrared light is applied, the cells swell and then burst, causing the cancer cell to die. Photoimmunotherapy is in clinical trials in patients with inoperable tumors.

How NIR-PIT Works

The new studies were led by Hisataka Kobayashi, M.D., Ph.D., of NCI's [Center for Cancer Research](#) (CCR), who [developed the NIR-PIT approach](#). NIR-PIT uses a specific antibody chemically joined to a photoabsorber, a molecule that absorbs light of a specific wavelength. The photoabsorber used in NIR-PIT, called IR700, absorbs light in the near-infrared part of the spectrum. Dr. Kobayashi engineered the antibody-photoabsorber combination, or conjugate, so that it is activated by near-infrared light only when bound to its target molecule. Near-infrared light is used because it can penetrate living tissue without causing damage.

"When the antibody-photoabsorber conjugate is injected into a mouse or human, it binds to the cancer cells [that overexpress the target for the antibody]. When near-infrared light is applied, the cells begin to swell rapidly and then burst... causing a form of rapid cell death called necrotic (or immunogenic) cell death," explained Peter Choyke, M.D., chief of CCR's [Molecular Imaging Program](#) and a collaborator on the studies. "Dr. Kobayashi has developed conjugates with many antibodies, and that opens up the possibility of treating a wide variety of cancers."

For example, Dr. Choyke said, because mesotheliomas are notoriously difficult to remove surgically, "one possible use [of the mesothelin antibody-IR700 conjugate] would be...to use NIR-PIT after surgery, to try to 'mop up' residual cancer that was missed by the operation."

Unleashing Killer T Cells

The study presented at the AACR meeting builds on another finding by Dr. Kobayashi and his colleagues. When tumor cells burst and die in response to NIR-PIT, the cells release their contents into the extracellular space. The healthy immune system adjacent to dying tumor cells detects this cellular debris as "foreign," resulting in activation of an immune response that further aids in destroying the cancer.

"We know that there are [immune cells called] T cells capable of destroying the cancer in the cancer's own microenvironment," Dr. Kobayashi said, "but they are suppressed by other immune cells called regulatory T cells (Tregs)."

To try to eliminate these immune-suppressing cells, the researchers attached IR700 to an antibody that targets Tregs. They injected the conjugate into mice with healthy immune systems that had tumors made up of mouse colon cancer or lung cancer cells implanted under their skin. When the tumors were exposed to NIR light, Treg cells were quickly and selectively removed from the microenvironment. This led, in turn, to rapid activation of tumor cell-killing T cells within an hour, tumor shrinkage within a day, and prolonged survival of the mice. Tregs in organs that were not exposed to NIR light were not affected by the treatment.

In this study, the researchers also saw cell-killing effects in implanted tumors that were distant from the

NIR light-treated tumor.

"In other words," Dr. Kobayashi explained, activated T cells from the treated tumor "traveled to other sites of tumors in the mouse and created significant responses in those tumors."

The advantage of the Treg-depleting approach, he noted, is that it is an alternative to developing a host of different antibodies, such as the anti-mesothelin antibody, to target molecules found on specific types of tumors. "There's only one type of Treg in the body, so the same antibody could be used for multiple tumor types. Moreover, by removing the immune-suppressing Tregs at one site you can get the killer T cells to become active throughout the body." Normal tissues in the mice are not harmed because NIR-PIT unleashes only the T cells that are programmed to kill the cancer.

Limitations and Next Steps

Like all cancer therapies, the NIR-PIT approach has limitations. Most obvious is the inability to get near-infrared light to all parts of the body. Although near-infrared light does penetrate tissue, it cannot penetrate deeply. One potential solution is to expose tumor tissue, like mesothelioma, to near-infrared light during surgery. Light could also be delivered to some tumors—for example, lung cancers—through a thin, tube-like device called an endoscope, or even via ultra-thin light fibers implanted into a tumor with a special surgical instrument.

Another limitation of these studies is that the mouse model of mesothelioma the researchers used in the first study, as well as mouse models they have used in studies of NIR-PIT for other cancers, was created by implanting human tumor tissue under the skin of mice with a greatly suppressed immune system. This type of model "does not fully represent human cancers," the researchers wrote in *Oncotarget*.

However, Dr. Kobayashi said, "we found that when we performed tumor-cell targeted NIR-PIT in animals with healthy immune systems we got much better responses. Therefore, we believe that the responses will be much more robust in people with intact immune systems than we saw in mice."

The ongoing phase I [clinical trial of NIR-PIT](#) may help answer that question. The trial, which is testing a conjugate of IR700 and cetuximab (Erbix®), an EGFR1 antibody, for patients with recurrent head and neck cancer, is being conducted by the San Diego-based Aspyrian Therapeutics, which licensed the technology from NCI.

The NCI researchers are hopeful that the trial will provide more definitive information on the promise of this new treatment approach. Meanwhile, additional research is needed to better understand the mechanism of tumor cell killing by NIR-PIT, Dr. Choyke said, an avenue that they are pursuing.

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